



Study of Cardiovascular Risk Prediction in Patients with Type 2 Diabetes with Arterial Hypertension after Combined Hypotensive Therapy of Enalapril with Moxonidine

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ABSTRACT

Introduction: Treatment of arterial hypertension in type 2 diabetes mellitus patients is complex and at the same time, according to our data, possible and/or controlled process. For example, the use of combined antihypertensive therapy of enalapril with moxonidine is effective in the treatment of arterial hypertension in patients with type 2 diabetes, which has a positive effect on the dynamics of catecholamine excretion and 3,4-dioxyphenylalanine, monoamine oxidase activity, significantly reduces the level of Malonaldehyde in serum.

Aim and Objective: After combined hypotensive therapy with moxonidine, we observed a more pronounced statistically significant decrease in daily excretion of CA and DOFA, with values of these indicators approaching those of the control group.

Result: Thus, after treatment with moxonidine, there was a significant decrease in SBP by 28.5%, DBP by 11.2% ($P < 0.001$), possibly due to suppression of the SAS functional activity.

Key Words: Type 2 diabetes with arterial hypertension, Catecholamine excretion, Monoamine oxidase, Dopamine

INTRODUCTION

The appearance of new antihypertensive agents has not led to an increase in the frequency of achieving the target AP level in AG monotherapy.¹⁻³ This fact is caused by the emphasis on combined therapy of AG. When choosing a drug for combined therapy of HA it is necessary to take into account the presence of risk factors, lesions of target organs, and associated clinical conditions.^{4,5,6} It has been revealed that certain antihypertensive medications of arterial pressure reduction can also influence metabolism. Moxonidine, sympatholytic, and agonist of imidazoline receptors of the central nervous system is an effective drug used to treat arterial hypertension.^{5,6} Several clinical studies have shown the efficacy of moxonidine in treating AG, which was comparable with the efficacy of other

modern antihypertensive drugs. Clinical studies presented in foreign literature indicate AD correction and cardioprotective effect when using this drug.^{7,8,9} There are also data on the reduction of insulin resistance when using this drug.^{10,11}

MATERIAL AND METHODS

This subgroup - B consisted of 20 patients who also received traditional treatment, consisting of diet (table 9), sugar-reducing therapy, antioxidants (Berlithione 600 units per day), in addition to hypotensive therapy (enalapril in a dose of 10 mg per day) received moxonidine (physiotens, Solvay Pharma) in doses of 0.2-0.4 mg during 12 weeks.

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RESULTS

After combined hypotensive therapy with moxonidine, we observed a more pronounced statistically significant decrease in daily excretion of CA and DOFA, with values of these indicators approaching those of the control group. Thus, the excretion of total A decreased by 20.4% (1.2 times), HA - by 25.6% (1.3 times), YES - by 8.9% (1.1 times), DOFA - by 25% (1.25 times) ($P < 0.01-0.001$). There was also a normalization of ratios of SCs, their precursors, and metabolites (Figures 1-3).

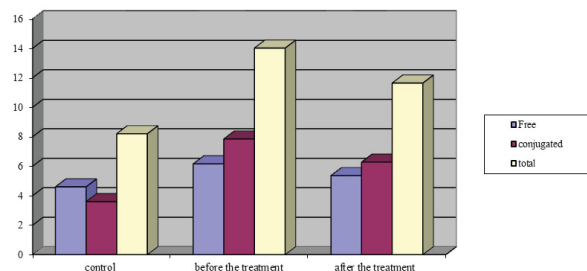


Figure 1: Daily adrenaline excretion in healthy and type 2 diabetes patients in combination with hypertension (subgroup B) before and after treatment with combined antihypertensive therapy.

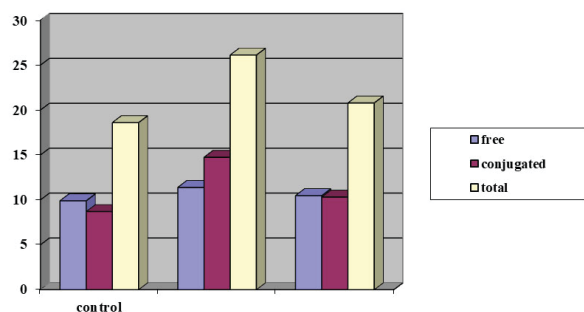


Figure 2: Daily excretion of norepinephrine in healthy and patients with type 2 diabetes in combination with hypertension (subgroup B) before and after treatment with combined antihypertensive therapy.

We also noted a more significant increase in MAO activity by 27.5% (1.4 times) ($P < 0.001$) about the indices of the initial level and the approach of these indices to the values of the control group (Fig. 3).

The results of the analysis of LPO processes showed that there is a significant decrease in the secondary products of LPO - MDA, the level of which decreased from 6.82 ± 0.44 nmol/ml before treatment to 4.43 ± 0.28 nmol/ml after treatment, which was 53, 8% (1.54 times). Post-treatment MDA values in this subgroup were significantly close to those in the control group.

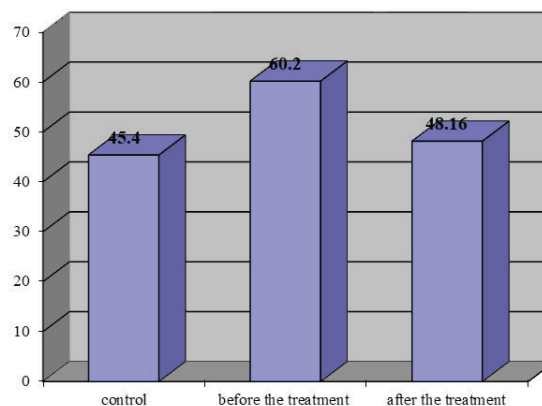


Figure 3: Daily excretion of DOPA in healthy people and patients with type 2 diabetes in combination with hypertension (sub-group B) before and after treatment with combined antihypertensive therapy.

Changes in all parameters of the lipid profile in subgroup B were statistically significant, except HDL cholesterol. The results of the treatment in subgroup B were characterized by a more significant decrease in the lipid spectrum of blood, so the level of total cholesterol decreased by 22.2% (1.23 times) ($P < 0.001$), there was a decrease in LDL cholesterol by 30.7%, (in 1, 31 times) ($P < 0.001$). The levels of cholesterol VLDL, TG is 14.4% (1.14 times) and 14.9% (1.15 times) less, respectively, similar indicators before treatment ($P < 0.01-0.001$). The atherogenic index is 35.1% (1.35 times) ($P < 0.01$), lower than the indicators of this subgroup of patients before treatment. The ratio of LDL cholesterol / HDL cholesterol decreased by 39.4% (1.39 times). The level of HDL increased by 6.5% ($P > 0.05$) about the indicators before treatment. In this regard, moxonidine, which suppresses the activity of the sympathoadrenal system and antioxidants that increase beta-oxidation of free fatty acids, act as synergists.

The average blood glucose level before treatment was 11.4 ± 0.74 mmol / L, and after treatment, 9.26 ± 0.65 mmol / L, i.e. the indicator after treatment decreased by 20.3% ($P < 0.01$).

Our studies have shown that a significant change in the LPO system immediately affects the SAS activity, which was expressed by a decrease in the daily excretion of adrenaline, norepinephrine, dopamine, DOPA, an increase in the level and improvement of the catalytic activity of MAO and the level of glucose in the blood. The indicators were sharply close to the values of the control group.

More clinically significant for assessing the effectiveness of antihypertensive therapy is the normalization of blood pressure, especially in patients with type 2 diabetes (Table 1).

Thus, after treatment with moxonidine, there was a significant decrease in SBP by 28.5%, DBP by 11.2% ($P < 0.001$), possibly due to suppression of the SAS functional activity

Table 1: SBP, DBP and glucose indices in subgroup B during treatment

AH in mm	Subgroup B (n=20)	
	Before the treatment	After the treatment
SBP	164.5±3.11	128.0±1.28*
DBP	94.5±1.74	85.0±0.98*
Glucose, mmol/L	11.4±0.74	7.26±0.65*

Note: * - $p < 0.001$

Combined antihypertensive therapy with moxonidine at a dose of 0.02-0.04 mg/day was well tolerated by patients. Not a single case of drug withdrawal due to unwanted side effects has been reported. 2 patients had a headache and dry mouth, which disappeared after a week and did not require discontinuation of the drug.

Thus, the addition of an imidazoline receptor agonist moxonidine (Physiotenza) to combination therapy in patients with type 2 diabetes seems promising, causes the desired improvement in the condition and is the drug of choice for this category of patients.¹²

Clinical example: patient N. Makhkamov, born in 1950, case history No. 5793/169, was admitted to the 6th therapeutic department of the AGMI clinics on 23.03.2005, was discharged on 02.04.2005.

Clinical diagnosis: Diabetes mellitus type 2, moderate, stage of decompensation. Donkey: Diabetic angiopathy of the lower extremities of the II stage, polyneuropathy of the I stage, periodontosis, retinopathy of the I stage, hepatosis.¹⁵⁻¹⁸

SOP: Hypertension stage 2, AH stage 2, risk of stage 3.

Complaints at admission: thirst, frequent urination, headaches, palpitations, pains and numbness in the legs, a feeling of "creeping", chilliness in the lower extremities, loss and loosening of the teeth.¹³⁻¹⁸

Anamnesis: Considers himself ill for 3 years, has repeatedly undergone a comprehensive examination and inpatient treatment. The disease is associated with stress. He takes hypoglycemic drugs (maninil, diabeton). For 8 years, he has been suffering from arterial hypertension, does not take antihypertensive drugs (enam, berlipril) regularly.¹⁹⁻²²

Genealogical history: not burdened.

Twice a year he receives inpatient treatment for the disease. He takes sugar-reducing drugs and other metabolic drugs (Mildronate, Riboxin, ATP, etc.).²³ During the last week,

the patient's state of health worsened, increased dry mouth, thirst, increased urination, more frequent headaches, palpitations, dizziness, and therefore, the patient was hospitalized in the 6th therapeutic department of the AGMI clinics.^{24,25}

Objectively: General condition of moderate severity. Consciousness is clear. Skin and visible mucous membranes of normal colour. The subcutaneous fat is overdeveloped. The patient's height is 170 cm, weight 100 kg, BMI = 34.6. Vesicular breathing in the lungs. The boundaries of the relative dullness of the heart are expanded to the left. Heart sounds are rhythmic, sharply muffled, the accent of the II tone on the aorta, systolic murmur at the apex. Pulse 90 beats per minute, rhythmic, full. Blood pressure 170/90 mm Hg. Art. Tongue dry, white-coated. The abdomen is soft, b / painful. Liver at the edge of the costal arch.

Chest fluoroscopy: pulmonary fields without features. Increased left ventricular arch.

ECG: sinus tachycardia, the horizontal position of the electrical axis of the heart, signs of left ventricular hypertrophy.

Blood test: Hb -100 g / l; er -3.7x10¹²; c.p. -0.8; L - 5.8x10⁹; ESR -9 mm / h

Urine analysis: protein - abc., Ep- 1-2-3 in the n / a; L -1-2-1 in p \ h; uric acid salts.

Coagulogram: PTI 80%; tolerance to heparin 5'; recalcification of plasma 175''; thrombotic 5; fibrinogen according to Rutberg 3125 mg / l.

Biochemical blood test: total bilirubin. -7.8 mmol / L, direct-abs., Not direct -7.8 mmol / l, blood glucose - 7.5 mmol / l, creatinine - 85 mmol / l, sugar 13.1 mmol / l.

Blood lipid spectrum: total cholesterol-7.4 mmol / l, LDL cholesterol - 5.6 mmol / l, HDL cholesterol - 0.9 mmol / l, VLDL cholesterol - 0.9 mmol / l, TG - 2.1 mmol / l, LDL-C / HDL-C - 6.22 units, IA-7.2 units.

Ultrasound: Hepatosis.

On the first day of admission to the clinic, the patient underwent a comprehensive examination of the daily excretion of catecholamines in the urine, determination of the activity of monoamine oxidase, and the level of malondialdehyde in the blood serum.

The results of the analyzes showed an increased level of daily excretion of CA and DOPA in the urine about the average values of the control group and the group of normotensive type 2 diabetes patients. Thus, there was an increase in the excretion of total A by 35.38%, and total AN by 43.11%.

As a result of the study, there is a slight increase in the excretion of total DA by 9.84%. The daily excretion of DOPA is increased by 19.82%. Along with this, a decrease in the DA / DOPA ratio by 19.6% relative to the control was also noted,

which may indicate the inhibition of DA biosynthesis. Indicators of the ratio HA / DA exceeded the indicators of the control group by 29.3%. The A / HA ratio was 4.6% lower than that of the control group. All this testifies to the impairment of CA biosynthesis from precursors. MAO activity was reduced by 57.1%. The MDA level is 36.4% higher than the indicators of the control group (Table 2.).

Table 2: Daily excretion of CA and DOPA in the urine, MAO activity and MDA level in the serum of the patient Makhkamova N., case history No. 5793/169

CA	Fractions	On the 2nd day of admission	After 12 weeks of treatment Control group	Control group (n=15)
E	Free	6.03	5.25	4.6
	Conjugated	5.07	4.06	3.6
	Total	11.1	9.30	8.2
NE	Free	6.6	6.07	9.9
	Conjugated	20.02	14.02	8.7
	Total	26.62	20.09	18.6
DA	Free	149	146.02	152.0
	Conjugated	167	143.62	135.7
	Total	316	289.64	287.7
Dopa		54.4	43.52	45.4
E/NE		0.42	0.46	0.44
NE/DA		0.084	0.069	0.065
DA/DOPA		5.81	6.66	6.34
MAO (unit/ext)		0.03	0.045	0.07
MDA (nmol / ml)		4.5	2.93	3.3

Thus, the functional state of the SAS inpatient N. Makhkamov was characterized by high hormonal activity, manifested by an increased level of A, HA, DA from precursors, and a parallel change in the coefficient ratios. The treatment was prescribed taking into account the effect on the functional state of the SAS in patients of this category.

The patient was prescribed traditional therapy for type 2 diabetes and combined antihypertensive therapy with an ACE inhibitor - enalapril in appropriate dosages, in combination with moxonidine. As a result of the treatment, within 12 weeks, we observed a statistically significant decrease in the daily excretion of CA and DOPA about the initial values (Table 19). Thus, the excretion of total A decreased by 19.33% (1.19 times), AN - by 32.5% (1.33 times), YES - by 9.10% (1.09 times), DOPA - by 25.0% (1.25 times). MAO activity reached 0.045 units/ext, which is 50.0% (1.5 times) higher than the initial indicators. There was a decrease in LPO indicators: the level of MDA was 53.6% (1.54 times) lower than

similar indicators before treatment (Table 19).

The parameters of the lipid spectrum in this patient are shown in table 20, after the treatment, the lipid spectrum decreased. So: total cholesterol was lower by 12.4% (1.12 times), LDL cholesterol - by 16.1% (1.16 times), HDL cholesterol - by 5.9% (1.06 times), VLDL cholesterol - by 9.09% (1.1 times), TG - by 9.6% (1.1 times), IA - by 23.4% (1.23 times) lower than the indicators before treatment.

As a result of our course of treatment, the patient has a change in the main parameters: a decrease in SBP and DBP levels due to a decrease in the functional activity of the SAS, an improvement in glucose and blood lipid spectrum, an increase in monoamine oxidase activity and a decrease in lipid peroxidation processes. However, the indicators slightly exceeded the values of the control group.

From the presented data, we can conclude that the use of traditional drug therapy, including a combination of antihypertensive drugs - enalapril and moxonidine in patients with type 2 diabetes with hypertension gives a significant clinical effect. Minor differences in CA parameters from the control group, which are more significant than in the patient who received monotherapy with enalapril, indicates the clinical efficacy of the combination of enalapril with moxonidine (Table 3).

Table 3: Indicators of the blood lipid profile of the patient Makhkamova N; case history No. 5793/169

Indicators	On the 2nd day of admission	After 12 weeks of treatment Control group	Control group (n=15)
Total cholesterol, mmol / l	7.4	6.07	4.0±0.2
LDL cholesterol, mmol / l	5.6	4.23	2.13±0.1
HDL cholesterol, mmol / l	0.9	1.06	1.2±0.13
HS VLDONP, Mol / L	0.9	0.78	0.25±0.02
TG, Mol / L	2.1	1.83	1.3±0.1
IA, units	7.2	4.7	2.6±0.14

So in this patient, the blood pressure indicators decreased from 170/100 to 130/85, which is 30.8% for SBP and 17.6% for DBP.

When studying the lipid spectrum as a result of treatment with the addition of moxonidine, a decrease in all its parameters is noted, so the level of total cholesterol after treatment decreased by 21.95%, LDL cholesterol decreased by 32.45%. Levels of cholesterol VLDL, TG were reduced by 15.38%

and 14.7%, respectively, in the same parameters before treatment. The atherogenic index was reduced by 53.2% about the indicators before treatment. The ratio of LDL cholesterol / HDL cholesterol was 3.9 and was lower by 59.0%. The level of HDL was increased by 17.8% of the parameters of this patient before treatment (Table 3).

As a result of the course of treatment, the patient shows a change in the main parameters: a decrease in the functional activity of the SAS, an improvement in the blood lipid spectrum, an increase in monoamine oxidase activity, and a decrease in lipid peroxidation processes. Indicators of the studied parameters of this patient after combined antihypertensive treatment with moxonidine practically did not differ from the values of the control group.

From the presented data and taking into account the literary background.¹³⁻¹⁵ It can be concluded that the addition of moxonidine to the combination therapy of hypertensive patients in combination with type 2 diabetes leads to a decrease in systolic and diastolic blood pressure, due to a decrease in SAS activity. Also, the inclusion of moxonidine promotes a decrease in metabolic risk factors, which gives a certain clinical effect and it can be used as the drug of choice in the combination therapy of hypertension in patients with type 2 diabetes.

DISCUSSION

According to our data, the combination therapy of enalapril with moxonidine gives a favourable (decrease in blood glucose in every fifth patient) metabolic effect (increases the sensitivity of tissues to insulin), leads to more significant changes (normalization of the functional activity of SAS and LPO processes). In patients with type 2 diabetes with hypertension, significant violations of the functional activity of the SAS were revealed, manifested in the activation, mainly of the hormonal link (clinically, there is a pronounced improvement in the general condition, metabolic blood parameters). In parallel, a pronounced decrease in the catalytic properties of MAO was established with the activation of lipid peroxidation processes. According to our hypothesis, the reason for the low activity of MAO is the excessive intensification of LPO processes. It has been proven that not only hyperglycemia but also hyperinsulinemia is involved in the mechanisms of increased oxidative stress in diabetes. Hyperglycemia with an increase in the rate of autooxidation of glucose leads to the formation of free radicals. Hyperinsulinemia activates SAS and the amount of catecholamine-induced formation of free radicals, and through a catecholamine-induced increase in NEFA, the formation of free radicals also increases and the level of glutathione decreases. Confirming the existing literature data, we suggest, possibly, that prolonged lipid peroxidation leads to the activation of the functional state of the

SAS, which in turn activates LPO itself, thereby creating a vicious circle showing the relationship and interdependence of these two systems.

The development of hypertension correction in type 2 diabetes is explained as follows: hyperactivation of SAS (activation of mechanisms regulating blood pressure level) → impaired HA metabolism → pronounced tissue hyper-sympathicotonia → sympathetic stimulation of the heart, blood vessels and kidneys → hypertension ↔ it is advisable to use drugs that reduce it (SAS) activation → combined AHT, together with an antioxidant, normalizes the excretion of CA and their metabolic precursor DOPA, MAO activity and LPO processes → this treatment tactic can be recommended as the basis of pathogenetic therapy in the treatment of AHPSD2.

CONCLUSIONS

The inclusion of combined antihypertensive therapy with ACE inhibitors with an imidazoline receptor agonist moxonidine in the basic therapy of type 2 diabetes patients with AH leads to an improvement in both the clinical manifestations of the disease and the indicators of SAS, blood lipid spectrum and LPO system. After combined AHT with antioxidants (vitamin E, α -lipoic acid), it was noted:

- 1) Significant increase in MAO activity (1.4 times $p < 0.001$);
- 2) A trend towards a decrease in the level of total cholesterol, TG and LDL cholesterol and an increase in the content of HDL;
- 3) Moxonidine (with a favourable metabolic effect) suppressing the activity of SAS and antioxidants that increase the beta-oxidation of free fatty acids act as synergists;
- 4) A significant decrease in the content of secondary products of LPO processes - malonic dialdehyde (1.54 times, $p < 0.001$);
- 5) The level of blood pressure is below 140/90 mm Hg. was noted in 80%, and a decrease in blood pressure below 130/90 mm Hg in 45% of patients with type 2 diabetes with hypertension.

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